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Letter to the Editor

Pulmonary vein isolation alone and combined with renal sympathetic denervation in CKD patients with paroxysmal AF: A sub group analysis

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Renal sympathetic denervation
Hypertension
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Chronic kidney disease

The ideal approach for the treatment of atrial fibrillation (AF) is rhythm control, but this is sometimes very hard to accomplish [1]. For such procedures, complete isolation of all pulmonary veins (PVs) is currently widely accepted as the best endpoint. Pokushalov and colleagues [2] recently reported that renal sympathetic denervation (RSD) reduces AF recurrences when combined with pulmonary vein isolation (PVI). RSD consists of a recent strategy using percutaneous catheter-based delivery of radiofrequency (RF) energy to interject the sympathetic innervation of the kidneys, and PVI is a well established ablation technique used to treat paroxysmal AF. RSD procedure exposed no severe vascular or renal complications in the long term (up to 36 months). Our group believes that RSD can reduce AF recurrence in patients with chronic kidney disease (CKD) by modulation of the sympathetic hyperactivity present in this disease. The goal of this prospective study was to compare the impact of PVI in controlled hypertensive patients with paroxysmal AF with and without CKD to PVI associated with RSD in controlled hypertensive patients with paroxysmal AF and moderate CKD.

This prospective, longitudinal study involved 145 patients with controlled hypertension and CKD, all of them having a history of symptomatic paroxysmal AF (PAF). The study was piloted in agreement with the Helsinki declaration and approved by the ethics committee of our institution. All patients signed the informed consent term before inclusion. This study was conducted at the Hospital e Clínica São Gonçalo, Rio de Janeiro, Brazil. Patients were recruited from January 2012 till January 2015 from the Arrhythmias and Artificial Cardiac Pacing Service of the same hospital. Enrolled patients met the following criteria: (i) mean 24-h systolic ambulatory blood pressure measurement (ABPM) of ≥100 and <130 mm Hg, (ii) essential hypertension for >1 year, (iii) a physically normal heart with an ejection fraction of >50% as measured by echocardiography (Simpson's method), (iv) PAF (defined as AF episodes lasting <7 days with spontaneous termination) registered on ECG or 24-h Holter monitoring, (v) aged 18 to 80 years, (vi) estimated glomerular filtration rate (eGFR) of >15 mL/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation6 (patients with eGFR >60 mL/min/1.73 m^2 were also required to have microalbuminuria), and (vii) the capacity to read, comprehend and sign the informed consent form, and attend the study. Patients with any of the following were excluded: (i) pregnancy; (ii) valvular disease with significant adverse sequelae; (iii) unstable angina, myocardial infarction, transient ischemic attack or stroke within the preceding six months; (iv) renovascular abnormalities; (v) psychiatric disease; (vi) allergy to ionic contrast medium; (vii) the inability to be monitored clinically after the procedure; (viii) a known addiction to alcohol or drugs that affects the intellect; (ix) a serious health condition that, in the investigator's opinion, may have adversely affected the safety and/or efficacy of the participant or the study (*e.g.*, abdominal aortic aneurysm, clinically significant peripheral vascular disease, diseases that might have caused bleeding due to thrombocytopenia, hemophilia, or significant anemia); (x) congestive heart failure (symptoms of functional class II to IV heart failure on the New York Heart Association scale); (xi) a previous AF ablation procedure; (xii) treatment with amiodarone.

The subjects were divided into two groups according to their KDIGO CKD status, and procedures performed: CKD patients underwent PVI (n = 96), and CKD patients underwent PVI + RSD (n = 49). All of them were followed at least 6 months to assess maintenance of sinus rhythm, to monitor variations in blood pressure and renal function. The primary endpoint of this study was a 30-s recurrence of AF recorded by the 24-hour-Holter monitoring. The blanking period (the first 3 months after ablation) was excluded from the analysis [3], and the 24-hour-Holter monitoring was evaluated at baseline and quarterly after the performance of procedures forward. The secondary endpoints were an evaluation of mean 24-h ABPM, eGFR (CKD-EPI) [4] and albuminuria at baseline and 6 months after the procedures. Additionally, in the subjects underwent RSD safety was evaluated by a renal arterial duplex scan at baseline and 6 months after this procedure.

The AF ablation procedure has been described in detail previously [5]. All patients underwent complete PVI using a three-dimensional mapping system (EnSite Velocity; St. Jude Medical) without additional ablation lesion sets or lines. Patients still in AF at the end of the procedure were converted to sinus rhythm by cardioversion.

The RSD procedure has been described in detail previously [6]. The patients remained hospitalized in the ward for 24 h after the procedure.

The results are expressed as a mean and standard deviation for normally distributed data and as median with interquartile range otherwise. Comparisons between two-paired values were performed with the paired t-test in cases of a Gaussian distribution and by the Wilcoxon test otherwise. For normality of distribution, D'Agostino-Pearson test was used. Comparisons between more than two-paired values were made by repeated-measures analysis of variance or by Kruskal–Wallis analysis of variance as appropriate, complemented by the post-hoc Tukey test. Categorical variables were compared with Fisher's exact test. A two-tailed P-value <0.05 was used as a criterion for statistical significance. Correlations between two variables were performed by Pearson's chi-square test in case of a Gaussian distribution and with the Spearman correlation test otherwise. Kaplan–Meier analysis was performed to determine the probability of success, estimated as the percentage of AF freedom. Differences in arrhythmia-free survival were assessed with the log-rank test. Cox regression analysis was applied to

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Table 1
General features of patients at baseline.

Parameters	CKD PVI	CKD PVI + RSD	Overall P-value
N	96	49	–
Age (years)	59 ± 15	63 ± 12	0.1075
Body mass index, kg/m^2	26.5 ± 5.8	24.8 ± 9.6	0.1868
Male sex (%)	65 (68%)	30 (61%)	0.4641
White ethnicity (%)	59 (61%)	28 (57%)	0.7204
Paroxysmal AF	96 (100%)	49 (100%)	–
Hypertension	96 (100%)	49 (100%)	–
Type 2 diabetes mellitus	36 (38%)	17 (35%)	0.8557
Hyperlipidemia	50 (52%)	32 (65%)	0.1574
Chronic kidney disease			
Stage 2	46 (48%)	18 (37%)	0.2199
Stage 3	21 (22%)	10 (20%)	>0.9999
Stage 4	29 (30%)	21 (43%)	0.1429
Creatinine, mg/dL	1.50 ± 0.12	1.54 ± 0.15	0.0838
eGFR, mL/min/1.73 m^2	50.1 ± 5.4	48.3 ± 7.5	0.0996
Albumin:creatinine ratio, mg/g	93 ± 16	98 ± 19	0.0974
Antihypertensive	2.4 ± 0.5	2.2 ± 0.9	0.0874
ACE-inhibitors/ARB	96 (100%)	39 (100%)	–
Diuretics	68 (71%)	33 (67%)	0.7048
DHP Ca^{++} channel blockers	31 (32%)	18 (37%)	0.7108
β-blockers	50 (52%)	23 (47%)	0.6011
Mean 24-hour ABPM, mm Hg			
Systolic	119 ± 8	122 ± 15	0.1180
Diastolic	79 ± 8	78 ± 13	0.5684
24-Hour-Holter monitoring			
Average heart rate, bpm	75 ± 10	72 ± 17	0.2052
Echocardiographic parameters			
Indexed left atrial volume (mL/m^2)	40.0 ± 8.2	39.8 ± 9.4	0.8951
IST (mm)	9.2 ± 2.4	9.0 ± 2.3	0.6311
LVPWT (mm)	9.3 ± 1.5	9.5 ± 1.8	0.4796
LVEF, Simpson (%)	66.5 ± 10.0	65.8 ± 12.8	0.7180
LVEDD (mm)	46.2 ± 5.1	47.0 ± 4.3	0.3487
LVESD (mm)	31.9 ± 8.0	31.0 ± 6.9	0.5038
LV mass index (g/m^2)	95.4 ± 18.5	94.3 ± 19.4	0.7395

Values are expressed as Mean ± SD; ABPM, ambulatory blood pressure measurements; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DHP, dihydropyridine; eGFR, estimated glomerular filtration rate; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVPWT, left ventricular posterior wall thickness; PVI, pulmonary veins isolation; RSD, renal sympathetic denervation.

explore factors of AF recurrences. All statistical analyses were performed using the program Graphpad Prism v 7.0 (Graphpad Software, La Jolla, CA, USA).

The general features of the groups of patients are listed in Table 1. The mean follow-up period for the 236 patients was 22.4 ± 12.1 months. No patient developed procedural complications related to PVI or RSD. Real-time renal artery images were performed at the end of the procedure to evaluate acute eventual structural changes regarding the RSD. Six months after the procedure, all patients in the RSD group underwent a Doppler scan of the renal arteries and showed no evidence of stenosis or flow limitation compared to the same exam at baseline. No significant change was observed on the mean 24-h ABPM and average heart rate 24-hour-Holter monitoring from baseline to 6 months within the same group. Nor has there been significant differences between the groups at the same time points. The effects of PVI alone or PVI + RSD on the creatinine concentration, eGFR, and albumin:creatinine ratio during the first 6-month follow-up are shown in Table 2.

Table 3
Hazard ratio for AF recurrence between the various stages of CKD evaluated by Log-rank test.

AF recurrence	Hazard ratio	95% confidence interval	P-value
PVI			
CKD 4 *vs.* CKD 3	1.031	0.589–1.806	0.9044
CKD 4 *vs.* CKD 2	8.571	4.199–17.490	<0.0001
CKD 3 *vs.* CKD 2	7.830	3.344–18.340	<0.0001
PVI + RSD			
CKD 4 *vs.* CKD 3	2.702	1.148–6.361	0.0212
CKD 4 *vs.* CKD 2	13.620	4.698–39.500	<0.0001
CKD 3 *vs.* CKD 2	18.140	3.313–99.360	0.0008
PVI vs. PVI + RSD			
CKD 4	2.282	1.261–4.128	0.0039
CKD 3	5.564	2.564–12.070	<0.0001
CKD 2	4.309	1.011–18.370	0.0483

AF, atrial fibrillation; CKD, chronic kidney disease; PVI, pulmonary veins isolation; RSD, renal sympathetic denervation.

During a mean follow-up period of 19.3 ± 10.9 months, AF recurrence was higher in CKD patients underwent PVI than in those submitted to PVI + RSD, hazard ratio [HR], 95% confidence interval [CI] and P value by Log-rank test, are showed at Table 3. There was difference related to AF reappearance in the comparison between patients with CKD submitted to PVI and PVI + RSD at stages of CKD 2, 3 and 4 by Log-rank test ($P < 0.0001$), Fig. 1.

We believe that during follow-up, AF recurrence was higher in CKD patients who underwent PVI than in those with CKD who underwent PVI + RSD, because of the greatest sympathetic hyperactivity inherent to advanced CKD stages, suggesting that RSD can suppress sympathetic overactivity and the associated arrhythmogenic foci. Although our data show an independent contribution of RSD to reduce AF recurrence in patients with controlled hypertension and CKD, our patient cohort was small, which could be seen as a limitation. To our knowledge, however, the present series is the first to address the efficacy of percutaneous renal artery denervation in patients with concurrently controlled hypertension, CKD, and AF.

The presence of AF hampers measurement of LV ejection fraction because of tachycardia and beat-to-beat (*i.e.*, R-to-R) LV filling variability. Our measurements could have been less precise because we did not use a three-dimensional single-beat ultrasound system. In addition, the use of Doppler echocardiography to assess damage in the renal arteries might also be seen as less than ideal. However, early complications

Table 2
Effects on blood pressure, heart rate and renal function during the follow-up period.

Parameters	CKD (n = 96) PVI		CKD (n = 49) PVI + RSD		Overall P-value baseline	Overall P-value 6th month	Overall P-value baseline *vs.* 6th month
	Baseline	6th month	Baseline	6th month			
Mean systolic 24-hour ABPM, mm Hg	119 ± 8	120 ± 10	122 ± 15	117 ± 13	0.1180	0.3049	0.11951
Mean diastolic 24-hour ABPM, mm Hg	79 ± 8	79 ± 5	78 ± 13	76 ± 9	0.5684	0.0727	0.0611
Average HR 24-hour-Holter, bpm	75 ± 10	73 ± 14	72 ± 17	70 ± 18	0.2052	0.6137	0.1232
Creatinine, mg/dL	1.50 ± 0.12*	1.60 ± 0.10	1.54 ± 0.15*	1.30 ± 0.14	0.0838	<0.0001	<0.0001
eGFR, mL/min/1.73 m^2	50.1 ± 5.4*	46.0 ± 5.0	48.3 ± 7.5*	56.3 ± 6.8	0.0996	<0.0001	<0.0001
ACR, mg/g	93.0 ± 16.0	97.2 ± 22.5	98.0 ± 19.0*	62.3 ± 21.2	0.0974	<0.0001	<0.0001

Values presented as Mean ± SD. ABPM, ambulatory blood pressure measurements; ACR, albumin:creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, heart rate; PVI, pulmonary veins isolation; RSD, renal sympathetic denervation. *P < 0.0001 CKD patients underwent PVI + RSD at baseline *vs.* 6th month.

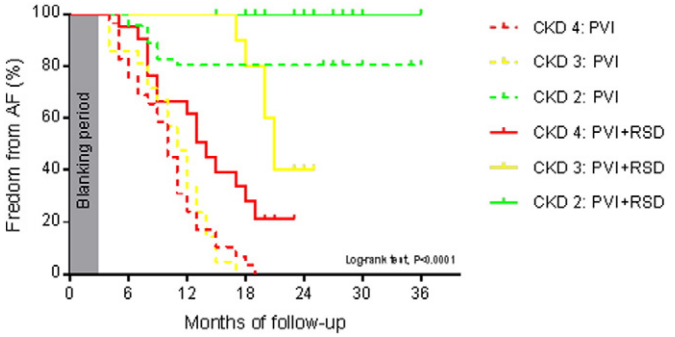

Fig. 1. Kaplan–Meier curves depicting recurrences of paroxysmal atrial fibrillation (AF) following pulmonary vein isolation (PVI) alone or combined with renal sympathetic denervation (RSD) in chronic kidney disease (CKD) patients.

due to the RF applications were excluded by angiography performed at the end of the procedure. Any other method, such as magnetic resonance angiography, computed tomographic angiography or further angiography of the renal arteries, could expose patients to additional undesirable toxic insults. Carbon dioxide angiography is not available at our institution.

More precise methods of eGFR assessment, such as cystatin C or iothalamate measurement, should be used in future studies to further evaluate our findings concerning the effects of RSD on the eGFR, especially considering that only one serum creatinine measurement was performed at each time point of the study. The neuromuscular sympathetic activity could also be measured, which would contribute greatly to the assessment of the degree of sympathetic blockade.

PVI + RSD are safe and appear to be superior to PVI in the treatment of paroxysmal AF in CKD patients. Although encouraging, our data are preliminary and need long-term validation in a large population. PVI + RSD are a potential tool for incorporation into future clinical practice.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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